Detailed Action

This office action is a response to applicant's communication submitted July 10, 2008 wherein rejections of record in the previous office action are traversed. This application claims benefit of provisional application 60/421004, filed October 24, 2002.

Claims 1-5, 9, 23, and 27-34 are pending in this application.

Claims 1-5, 9, 23, and 27-34 as amended are examined on the merits herein.

Applicant's arguments, submitted July 10, 2008, with respect to the rejection of claims 1, 9, and 28 under the doctrine of obviousness-type double patenting for claiming the same invention as claims 1, 6, and 17 of US patent 6020358 in view of Omogui et al., have been fully considered and found to be persuasive to remove the rejection as the claims of '358 do not specifically name complex regional pain syndrome. Therefore the rejection is withdrawn.

Applicant's arguments, submitted July 10, 2008, with respect to the rejection of claims 1, 9, and 28 under the doctrine of obviousness-type double patenting for claiming the same invention as claims 1, 4, 10, and 15 of US patent 6011050 in view of Omogui et al., have been fully considered and found to be persuasive to remove the rejection as the claims of '050 do not specifically name complex regional pain syndrome. Therefore the rejection is withdrawn.

The following rejections of record in the previous office action are maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9, and 27-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Omoigui (US patent publication 20040038874, of record in previous action) in view of Muller et al. (US patent 6020358, of record in previous action)

Omoigui discloses a method for the treatment of persistent pain by administering a drug that antagonizes one or more mediators of inflammation. (p. 1, paragraph 0004) Drugs useful in this manner include TNF-α blockers (p. 2, paragraphs 0007 and 0011) including thalidomide and thalidomide analogs. (p. 3, paragraph 0023) Reflex Sympathetic Dystrophy, otherwise known as chronic regional pain syndrome, is listed as a disease treatable by this method. (pp. 9-10, paragraphs 0078-0082)

Omoigui does not disclose a therapeutic method comprising administering the specific TNF-α inhibitor (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindolone-1,3-dione, or one involving a pharmaceutical dosage form having the specific limitations of instant claims 28-34.

Muller et al. discloses that compounds of a general formula including that of the claimed compound (column 5, line 1) are capable of decreasing the levels of TNF-α in a patient, (column 4, lines 55-67) thus qualifying as a TNF-α blocker. Example 12 (column 14, lines 35-55) is the exact same compound (+)-2-[1-(3-ethoxy-4-

methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindolone-1,3-dione disclosed in the instant claims. Muller et al. also discloses oral dosage forms of this compound as tablets or capsules, having a unit dosage of 1-100 mg, along with another dosage form in isotonic saline, a pharmaceutically acceptable solvate. (column 9, lines 22-52) Muller et al. also discloses that this chiral compound can be isolated as individual isomers and used in the disclosed invention, and additionally suggests methods for isolating the isomers. (column 8 line 63 - column 9 line 12)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the compound of example 12 of Muller et al. in the method of Omoigui, in an appropriate dosage form as disclosed by Muller et al. One of ordinary skill in the art would have been motivated to use this compound and dosage form because it is disclosed by Muller et al. to be useful for lowering TNF-α levels in a subject. One of ordinary skill in the art would reasonably have expected success because the scope of Omoigui includes all compounds capable of inhibiting or otherwise blocking the activity of TNF-α.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted July 10, 2008, have been fully considered as regards the above grounds of rejection and not found to be persuasive to remove the rejection. Applicant argues that there is not a motivation in the prior art to use the specific compound recited in the claims and taught by Muller as a therapeutic compound for treating complex regional pain syndrome (CRPS). This compound is clearly taught by Muller as a TNF-alpha inhibitor, as discussed above.

Therefore any defect in the prior art references must lie with Omogui. Applicant's traversal relies upon the assertion that Omogui's identification of TNF-alpha blockers such as thalidomide and thalidomide analogs as being useful for treating the identified pain disorders is somehow lacking. This argument appears to hinge on the large number of disorders and classes of compounds taught by Omogui. As indicated in the previous office action, the mere recitation of a large number of different alternatives by the prior art does not constitute a teaching away from any one particular alternative, or remove the expectation of success in practicing the invention. One of ordinary skill in the art would be able to practice any of the embodiments of Omogui et al. using the disclosed classes of compounds, for example TNF-alpha blocking thalidomide analogs, and furthermore to select any prior art disclosed TNF-alpha blocking thalidomide analogs to use in this method. As regards the decision to use the particular compounds of Muller et al., these compounds are clearly disclosed as TNF-alpha blockers by Muller et al., and so would be clearly useful in this manner in the invention of Omogui. Furthermore one of ordinary skill on the art would regard them as being thalidomide analogs. Although, as discussed in the previous office action, the motivation to use these compounds in this manner is based primarily on their disclosed TNF-alpha blocking activity, the structural similarity to thalidomide, while not the primary factor in making the combination, is close enough to add to the expectation of success of one of ordinary skill in the art.

Applicant further argues that Muller does not give a motivation or reasonable expectation of success for using the specific claimed enantiomer, citing *Forest Labs,*

INC vs. Ivax Pharmaceuticals, INC to demonstrate that an isolated enantiomer can be patentable over the racemic mixture. However, Muller does more than simply disclose the racemic mixture. Muller discloses a class of compounds having the same chiral carbon skeleton as the instantly claimed compound, as well as a specific compound which is identical to the racemate. Muller then specifically recognizes that these compounds have a chiral center, and explicitly suggests isolating and using the individual enantiomers. Muller then further suggests ways to isolate this enantiomer, including chiral chromatography and conjugation with a chiral acid. In view of this disclosure, one of ordinary skill in the art would clearly be motivated to use these individual enantiomers and would be able to isolate them by the suggested methods with a reasonable expectation of success. Doing so would not be a decision out of the blue to hunt for specific active enantiomers, but rather a decision to follow directions specifically laid out by the prior art reference.

For these reasons the rejection is deemed proper and made **FINAL**.

Claims 2-5 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Omoigui (US patent publication 20040038874, of record in previous action) in view of Muller et al. (US patent 6020358, of record in previous action) as applied to claims 1, 9, and 27-34 above, and further in view of Merck. (Reference of record in previous office action)

The disclosure of Omoigui in view of Muller et al. is discussed above. Omoigui in view of Muller et al. does not disclose a method further comprising administering the additional therapeutic agents of instant claims 2-5 or the therapies of instant claim 23.

Merck discloses that complex regional pain syndrome may be treated with several drugs including nifedipine, prednisone, opioid analgesics, tricyclic antidepressants, and anticonvulsants. (p. 1373, left column, second paragraph) It should be noted that it is well known in the art that opioid analgesics include oxycodone, tricyclic antidepressants include amitryptyline, imipramine, and doxepin, and anticonvulsants include gabapentin. Merck also discloses that physical therapy is essential throughout therapy for complex regional pain syndrome (p. 1373, left column, last paragraph) and that pain relief that outlasts the administration of a sympathetic block but is still transitory suggests the need for surgery. (p. 1373, left column, second paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Omoigui et al. for the treatment of complex regional pain syndrome further comprising administering one or more of the pharmaceutical active agents described by Merck and still further administering physical therapy and/or surgery. One of ordinary skill in the art would have been motivated to combine these teachings because Omoigui et al. and Merck both disclose their respective teaching as being useful for treating the same condition, namely complex regional pain syndrome. One of ordinary skill in the art would reasonably have expected success because combining two treatments known in the prior art to be effective for treating the same

disorder by different methods is reasonably expected to produce at least additive effects.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted July 10, 2008, have been fully considered as regards the above grounds of rejection and not found to be persuasive to remove the rejection. Applicant's arguments with respect to this rejection are the same as those made with respect to the rejection over Omoigui et al. in view of Muller et al., and are not found to be persuasive for the same reasons. Therefore the rejection is deemed proper and made **FINAL**.

Conclusion

No claims are allowed in this application. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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10/16/2008

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